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## **Recent advances in primary cutaneous T-cell lymphoma**

DeSimone, Jennifer A ; Sodha, Pooja ; Ignatova, Desislava ; Dummer, Reinhard ; Cozzio, Antonio ;  
Guenova, Emmanuella

**Abstract:** PURPOSE OF REVIEW Cutaneous T-cell lymphoma (CTCL) is a heterogeneous group of skin-homing T-cell neoplasms, which represent approximately 75% of all primary cutaneous lymphomas. Currently available drug therapies, when effective, simply control disease and the only option for curing CTCL is stem cell transplant. **RECENT FINDINGS** In the last year, there has been an incredible effort made to improve the understanding and treatment of CTCL. Recent findings indicate that epigenetic aberrations are integral to active disease. Furthermore, multiple tumor-derived immunological factors have also been shown to inhibit viability, proliferation, and cytokine production of nonmalignant T cells. Several novel targeted therapies show great potential, most promising being antibody drug conjugates targeting surface markers such as CD30 in some CTCL subtypes. Additional attractive targets involve the global modulation of epigenetic markers such as demethylation agents or HDAC inhibitors, either as single agents or in combination therapies. **SUMMARY** This is a concise review of recent advances in the field of CTCL with special focus on research articles over the preceding year.

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# Recent advances in primary cutaneous T-cell lymphoma

Jennifer A. DeSimone<sup>a</sup>, Pooja Sodha<sup>a</sup>, Desislava Ignatova<sup>b</sup>,  
Reinhard Dummer<sup>b</sup>, Antonio Cozzio<sup>b</sup>, and Emmanuella Guenova<sup>b</sup>

## Purpose of review

Cutaneous T-cell lymphoma (CTCL) is a heterogeneous group of skin-homing T-cell neoplasms, which represent approximately 75% of all primary cutaneous lymphomas. Currently available drug therapies, when effective, simply control disease and the only option for curing CTCL is stem cell transplant.

## Recent findings

In the last year, there has been an incredible effort made to improve the understanding and treatment of CTCL. Recent findings indicate that epigenetic aberrations are integral to active disease. Furthermore, multiple tumor-derived immunological factors have also been shown to inhibit viability, proliferation, and cytokine production of nonmalignant T cells. Several novel targeted therapies show great potential, most promising being antibody drug conjugates targeting surface markers such as CD30 in some CTCL subtypes. Additional attractive targets involve the global modulation of epigenetic markers such as demethylation agents or HDAC inhibitors, either as single agents or in combination therapies.

## Summary

This is a concise review of recent advances in the field of CTCL with special focus on research articles over the preceding year.

## Keywords

cutaneous T-cell lymphoma, epigenetics, microRNA, targeted therapies, Th2

## INTRODUCTION

Cutaneous T-cell lymphoma (CTCL) is a heterogeneous group of skin-homing T-cell neoplasms, which represent approximately 75% of all primary cutaneous lymphomas. Mycosis fungoides and Sézary syndrome comprise roughly 53% of all CTCL [1<sup>••</sup>]. The second most common CTCL type after mycosis fungoides, cutaneous CD30+ lymphoproliferative disorders, comprises 30% of CTCLs, and includes cutaneous anaplastic large cell lymphoma and lymphomatoid papulosis [2,3]. Roughly 3% of CTCLs are comprised of other rare subtypes: subcutaneous panniculitis-like T-cell lymphoma (SPTCL) includes those with the  $\alpha/\beta$  T-cell phenotype [4], whereas lesions with gamma-delta ( $\gamma\delta$ ) T-cell phenotype are subcategorized as primary cutaneous  $\gamma\delta$  T-cell lymphoma [5]. Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma [6], extranodal NK/T-cell lymphoma [7], aggressive epidermotropic cutaneous CD8+ lymphoma [8], angioimmunoblastic T-cell lymphoma [9], hydroa vacciniforme-like cutaneous T-cell lymphoma [10], and peripheral T-cell lymphoma, not otherwise

specified (PTCL-NOS) are other rarer subtypes of CTCL [11]. The clinical picture and prognosis in CTCL varies widely based on disease subtype and stage (adapted from the WHO-EORTC classification of CTCL based on clinical course) [12].

- (1) Indolent primary cutaneous T-cell lymphomas
  - (a) Mycosis fungoides
  - (b) Mycosis fungoides variants
    - (i) Folliculotropic mycosis fungoides
    - (ii) Pagetoid reticulosis
    - (iii) Granulomatous slack skin
  - (c) Primary cutaneous CD30+ lymphoproliferative disorders

<sup>a</sup>Department of Dermatology, Washington Hospital Center, Georgetown University, Washington, DC, USA and <sup>b</sup>Department of Dermatology, University Hospital of Zürich, Zürich, Switzerland

Correspondence to Emmanuella Guenova, MD, PhD, Department of Dermatology, University Hospital of Zürich, Gloriastrasse 31, 8091 Zürich, Switzerland. Tel: +41 44 255 5528; e-mail: emmanuella.guenova@usz.ch

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## KEY POINTS

- No unifying genetic mutation has been identified in CTCL; however, epigenetic aberrations are integral to active disease.
- Activation of immune mechanisms supporting Th1 responses is a promising strategy in the treatment of CTCL.
- Creatively designed trials are needed to examine multiple variables in this very small population to examine the utility of specific therapies and the efficacy of combination regimens, which may afford improved survival.

- (i) Primary cutaneous anaplastic large cell lymphoma
  - (ii) Lymphomatoid papulosis
- (d) Subcutaneous panniculitis-like T-cell lymphoma
- (e) Peripheral T-cell lymphoma (not otherwise specified)
  - (i) Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma
- (2) Aggressive primary cutaneous T-cell lymphomas
  - (a) Extranodal NK/T-cell lymphoma, nasal type
  - (b) Peripheral T-cell lymphoma (not otherwise specified)
    - (i) Aggressive epidermotropic cutaneous CD8+ lymphoma
    - (ii) Primary cutaneous gamma/delta T-cell lymphoma
    - (iii) Primary cutaneous angioimmunoblastic T-cell lymphoma
    - (iv) Hydroa vacciniforme-like cutaneous T-cell lymphoma

The most common variant, mycosis fungoides, generally behaves as a low-grade lymphoma with an indolent disease course. Most mycosis fungoides patients (70%) have early-stage disease (stage IA–IIA) at the time of the initial diagnosis however, a small subset progress and develop tumors and extracutaneous dissemination of malignant T cells [13]. Treatment selection is based on the body compartment(s) involved. Skin-directed therapies include topical drugs, phototherapy, and radiation and are appropriate for limited cutaneous involvement. Systemic agents are utilized in treating blood and lymphatic disease. Currently available drug therapies, when effective, simply control disease and the only option for curing CTCL is stem cell transplant.

## BIOLOGY OF CUTANEOUS T-CELL LYMPHOMA

The cause of CTCL is not entirely understood; however, it is recognized that widespread immune dysfunction is a hallmark of advanced disease [14] and emerging data suggest a role for epigenetic alterations in the pathophysiology of CTCL [15].

## RECENT MOLECULAR AND GENOMIC STUDIES

A mutation clearly linked to clinical disease in CTCL has yet to be discovered. Recently, a wide array of gene expression changes has been observed. However, these aberrant expression patterns are usually not caused by DNA sequencing mutations, and are instead the products of aberrant genome transcription, implicating epigenetic shifts in the pathophysiology of CTCL. There is mounting molecular evidence of epigenetic shifts in CTCL in observations of gene expression changes, microRNA (miRNA) dysregulation, altered methylation at gene promoters, and activity of histone deacetylases.

Somatic mutations in *PLCG1* (gene, coding for phospholipase C, gamma 1) have recently been identified by Vaqué *et al.* [16] in 19% of tissue samples from 42 mycosis fungoides patients. Increased downstream signaling toward nuclear factor of activated T cells activation was observed in the *PLCG1* mutants and inhibition of this pathway interrupted CTCL cell proliferation. The authors proposed that acquisition of *PLCG1* mutations may lead to permissive expansion of CTCL clones [16].

Intriguing are also the studies by Hashikawa *et al.* [17] aimed to identify the mechanism for epidermotropism in mycosis fungoides and adult T-cell leukemia/lymphoma (ATLL). Mycosis fungoides and ATLL can be clearly differentiated via complementary cDNA microarray analysis of epidermis and dermis. Downstream upregulation of skin-homing chemokines and chemokine receptors has been observed, and increased expression of lymphotoxin  $\beta$ , CCL21, and CCR10 is found in mycosis fungoides, whereas CCR4 and CLA expression is higher for ATLL [17].

miRNAs are small noncoding RNA molecules that regulate posttranscriptional gene expression. Several recent miRNA studies document aberrant expression of miRNAs in CTCL. In Sézary syndrome patients, multiple measurable miRNA changes are observed secondary to alterations in a chromatin region DN3 [18]. Upregulation of miR-155, miR-92a, and miR-93 has been observed in skin lesions of tumor-stage mycosis fungoides [19]. Mishra and Garzon [20] show that mi-R150 is

significantly downregulated in advanced CTCL, and that this downregulation is strongly associated with tumor invasion/metastasis. McGirt *et al.* [21] found reduced levels of miR-223 in blood from late-stage mycosis fungoides/CTCL and later observed therapeutic restoration/increase in miR-223 (as well as increased miR191 and miR-342) at 3 months post-extracorporeal photophoresis, which was also predictive of a clinical response.

Malignant T lymphocytes in CTCL have been shown to display widespread promoter hypermethylation associated with inactivation of several tumor suppressor genes [22]. CD158 (KIR3DL2), DNMT3, PLS3, and TWIST1 are all highly expressed in mycosis fungoides/Sézary syndrome and represent a pattern unique to CTCL [15]. Interestingly, these genes all have large CpG islands and loss of methylation may be a mechanism for activation of these genes. Further supporting this notion, hypomethylation of CpG islands was identified in CTCL patients [23]. Ferrara *et al.* [24] evaluated methylation patterns in 41 mycosis fungoides patients with Stage 1 disease, looking for patterns linked to increased risk of progressive disease over 12 years of follow up-observation. Distinct methylation patterns at four specific loci – LINE-1, PPARG, SOCS1, and NEUROG1 – were observed in the patients who progressed to advanced disease and matched the methylation profile seen in the Sézary-derived HUT78 cell line [24]. The role of histone deacetylases (HDACs) in the pathophysiology of CTCL has not been widely investigated. One study examined silent information regulator type-1 (SIRT1), the most known member of the Sirtuin (Sir2) family of nicotinamide dinucleotide-dependent class III HDACs, and found that SIRT1 is strongly expressed in both blood and lesional skin in CTCL [25].

These emerging data provide evidence that epigenetic aberrations are integral to active disease in CTCL and suggest that treatment strategies should be aimed at regulating multiple epigenetic target points, possibly through combination regimens.

## RECENT IMMUNOLOGICAL STUDIES

CTCL represents malignancies of skin-homing T cells, and widespread immune dysfunction is a hallmark of advanced disease. A recent comprehensive analysis of the cytokine production of T cells from leukemic CTCL identifies both malignant and benign T cells in patients with CTCL to be strongly Th2-biased. This bias proved to be intrinsic in malignant cells but extrinsic in benign T cells. Th2 cytokine production by the malignant clone seems to directly suppress Th1 responses in CTCL patients,

and inhibition of Th2 cytokines leads to recovery of protective Th1 immune responses [26]. Besides Th2 cytokines, tumor-derived galectins have also been shown to inhibit viability, proliferation, and Th1 cytokine production of nonmalignant T cells [27]. A study from Thode *et al.* [28] further documents important changes in the epidermis, including hyperproliferation and loss of the epidermal barrier function to be driven by tumor-derived galectins in CTCL. Early CTCL lesions, and especially mycosis fungoides, often clinically resemble skin lesions of atopic dermatitis – another Th2-mediated chronic skin disease [29]. In atopic dermatitis, reduced production of antimicrobial peptides in the skin accounts for frequent infections and impaired cutaneous immune response. Of interest are two studies by Suga *et al.* and Wolk *et al.* [30,31] that show lower expression levels of antimicrobial peptides in lesional CTCL skin. Beside tumor-derived galectins, low level of antimicrobial peptides in CTCL, as in atopic dermatitis, correlated with barrier dysfunction and frequent infections of the skin. *Staphylococcus aureus* is a common infectious agent, frequently found in cutaneous CTCL lesions. Krejsgaard *et al.* [32] could demonstrate that staphylococcal enterotoxin can further drive the immune dysregulation in CTCL patients by inducing a cross-talk between malignant and benign T cells that leads to signal transduction and activation of transcription (STAT3)-mediated production of immune suppressive interleukin-10 by the malignant T cells. STAT3 is constitutively phosphorylated and can further be activated in Sézary syndrome cells by interleukin-21 [33]. Thus, both STAT3 and interleukin-21 are potential targets of interest in the treatment of Sézary syndrome [34].

Recently, two further new cytokines have been proposed to play a role in the pathogenesis of mycosis fungoides and Sézary syndrome. A study by Ohmatsu *et al.* [35] demonstrates elevated interleukin-32 mRNA expression levels in mycosis fungoides and suggests that interleukin-32 might contribute to the disease progression. Another study from Singer *et al.* [36] reports on elevated serum levels of interleukin-31 in 14 of 26 pruritic Sézary syndrome patients. In three out of three patients with detectable malignant T-cell clone, the malignant cells were the predominant producers of interleukin-31 and the clinical resolution of pruritus correlated with decreased interleukin-31 levels in the circulation [36].

## RECENT THERAPEUTIC ADVANCES IN CUTANEOUS T-CELL LYMPHOMA

Although there is no unified international algorithm for the treatment of CTCL, there are several



novel therapeutic options to treat CTCL, with increasing interest in the development of targeted therapies [37,38].

As mycosis fungoides, the most common form of CTCL in all age groups, presents frequently with patch and plaque-stage disease, skin-directed therapies are considered first-line. More recently, the use of 308-nm excimer laser to treat early-stage (IA–IIA) disease was examined in a small group of six patients with less than 10% body surface area involvement refractory to topical therapy. Complete response was seen in 50% of patients [39<sup>¶</sup>]. This modality may be useful in targeting treatment to anatomically difficult intertriginous regions while reducing phototoxicities [39<sup>¶</sup>]. Brachytherapy is another well tolerated and effective therapeutic approach for difficult regions, such as the delicate facial skin. We recently conducted a clinical trial aimed to examine the overall clinical response to low-dose high-dose-rate brachytherapy in mycosis fungoides. In 10 patients and 23 facial mycosis fungoides lesions treated with brachytherapy, a complete response occurred in six patients (13 lesions) and a partial response in four patients (10 lesions) [40].

Refractory disease and advanced-staged disease often require systemic therapy. Systemic therapies include a number of newly emerging treatments with increasing effectiveness in stabilizing disease.

## THE EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER

Cutaneous Lymphoma Task Force recently presented the data from two important international CTCL clinical trials. The European Organization for Research and Treatment of Cancer (EORTC) trial 21011 was a randomized, open-label phase III trial evaluating the safety and efficacy of targret in capsules combined with psoralens in combination with ultraviolet light (PUVA) compared with PUVA alone in patients with stage IB-IIA CTCL [41]. No significant difference in response rate or response duration was observed; however, a trend toward fewer PUVA sessions and lower UVA dose required to achieve a complete clinical response was seen in the combination arm [41]. EORTC trial 21012 was a phase II clinical trial with intravenous pegylated liposomal doxorubicin mono-chemotherapy in patients with advanced mycosis fungoides (stage IIb, Iva, IVb) [42]. A total of 49 patients were treated on days 1 and 15 of a 28-day cycle for a median of 5 cycles. The overall response rate was 40.8% and median time to progression and median duration of response were 7.4 and 6 months, respectively [42].

Vorinostat and romidepsin, two histone deacetylase inhibitors (HDIs) that are FDA-approved for

the treatment of CTCL, have shown efficacy in treating relapsing CTCL and in providing extended response times. Studies to understand the response mechanisms have shown that HDIs induce cell cycle arrest and promote apoptosis, though resistance by suppression of proapoptotic proteins has been shown *in vitro* [43]. Overall response rate for both agents is approximately 33–34% with a durable response of 12–15 months at best [44,45]. The most common side-effects are weight loss, weakness, hematologic abnormalities namely anemia and thrombocytopenia, nausea/vomiting, and increased risk of infections [45,46]. Panobinostat is a pan-deacetylase inhibitor, which was studied in 179 bexarotene-exposed and bexarotene-naïve patients with CTCL at a dose of 20 mg orally three times per week [47]. The overall response rate was 17.3%. Reduction in the baseline mSWAT scores were observed in 74.1% of the patients and the median duration of response was 5.6 months in the bexarotene-exposed patients and was not reached at data cutoff in the bexarotene-naïve patients. Reported adverse events include thrombocytopenia, diarrhea, fatigue, and nausea [47].

Alemtuzumab, an anti-CD52 monoclonal IgG antibody FDA-approved for the treatment of relapsed and refractory cutaneous lymphoma, has shown efficacy in the treatment of advanced mycosis fungoides and Sézary syndrome, though there is an association with use of this drug and large cell transformation [48<sup>¶</sup>]. Interestingly, overall response rates in Sézary syndrome (70%) were higher than in mycosis fungoides (25%), suggesting that the systemic treatment is in fact better in targeting circulating T cells than memory cells residing in the skin [48<sup>¶</sup>,49]. Limiting factors in the use of alemtuzumab include profound lymphopenia conferring increased risk of systemic infections, ischemic colitis, and capillary leak syndrome [48<sup>¶</sup>].

Pralatrexate is a novel inhibitor of dihydrofolate reductase with greater antitumor effect than methotrexate because of increased internalization by tumor cells [46]. The overall response rate in one study assessing dose de-escalation while treating both advanced mycosis fungoides and Sézary syndrome was 41%, with higher doses noted to have an overall survival of 51% [46]. In patients that had progression of disease on methotrexate, a response rate of 46% was seen, suggesting that another mechanism of action may allow pralatrexate to exert its effect [46]. Common adverse events included mucositis, fatigue, nausea, fevers, anorexia, edema, and anemia, which were balanced with efficacy at a dose of 15 mg/m<sup>2</sup> [46].

Data on the effect of brentuximab – an antibody–drug conjugate of anti-CD30 monoclonal

antibody and the proapoptotic antitubulin agent monomethylauristatin – in CD30-positive mycosis fungoides, primary cutaneous ALCL, and other rare CD30-positive cutaneous entities are currently being collected [50–52]. A phase III trial in CTCL is currently recruiting patients. Interim results of a phase II open-label trial reported an overall response rate of 44% and mean duration of response of 12 weeks to brentuximab in 27 CD30+ mycosis fungoides patients (International Investigative Dermatology Meeting, Edinburgh, Scotland, 2013). Most recently, progressive multifocal leukoencephalopathy (PML) with lethal outcome has been reported in patients receiving brentuximab for Hodgkin lymphoma (three patients), primary cutaneous anaplastic large cell lymphoma (one patient), and transformed CD30+ mycosis fungoides (one patient). The three Hodgkin lymphoma patients and the mycosis fungoides patient developed progressive neurological deterioration and died soon after the development of the PML [53].

Chemokine receptor 4 (CCR4) is expressed by T cells and is important for their recruitment to the skin [54]. Mogamulizumab is a monoclonal antibody against CCR4 that has been developed for the treatment of diverse hematological malignancies and asthma [55]. Data from a recent multicenter phase II trial of mogalizumab in patients with relapsed peripheral T-cell lymphoma and CTCL have been published. Objective response was reported in 13 out of 37 patients (35%) with median progression-free survival of 3 months [56]. A phase III trial is open and actively enrolling patients.

Topical agents that have the ability to activate the innate immune system have recently been revisited in the treatment of mycosis fungoides [57]. Current clinical trials focus mainly on resiquimod – a TLR 7/TLR 8 agonist; cytosine-phosphate-guanine (CpG) – a TLR9 agonist – has demonstrated efficacy in CTCL in a phase I clinical trial [58].

## CONCLUSION

Recently, there has been an incredible effort made to improve the understanding and treatment of CTCL. Several novel targeted therapies show great promise; multiple recently discovered proteins seem to be important in the pathogenesis of CTCL and may have important implications for the development of new drugs.

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## Conflicts of interest

None.

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- of special interest
- of outstanding interest

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